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# RADIUM TOXICITY PROGRAM: A PROGRESS REPORT OF CLINICAL STUDIES ON TWENTY-FOUR PATIENTS

by

The Radium Toxicity Group
Report compiled and written by William B. Looney*

## 1. INTRODUCTION

In the summer of 1950, the Biological and Medical Research, Health Services, and Radiological Physics Divisions began a study of a group of mental patients given radium chloride intravenously by Schlundt, Nerancy, and Morris[1] at the Elgin State Hospital during 1930 and 1931. The data that are presented are the results of the coordinated effort of the following men and their associates: Austin M. Brues, Leonidas D. Marinelli, Robert J. Hasterlik, John E. Rose, William P. Norris, and Andrew F. Stehney. The writer, with Dr. Hasterlik and Dr. Brues, has been concerned with the clinical aspects and their correlation with various other types of laboratory observations. The detailed work in Sections 4 and 5 on localization of radium in relation to radiological and anatomical changes in bone was carried out by the writer with the collaboration of Dr. James S. Arnold and others. This is a progress report that summarizes the present state of the investigation. Detailed publication of various aspects will follow.

## 2. CLINICAL STUDIES

The clinical studies consist of observations made on twenty-four patients. Fourteen of these patients received radium chloride intravenously at the Elgin State Hospital during 1930 and 1931 (Table 1) and are still living at the institution. The remaining ten are patients who are living in the Chicago area and who received radium chloride either intravenously, intramuscularly, or orally. Two of the ten patients did not know that they had been given radium.

We are reasonably sure that radium, administered orally or parenterally, was not used extensively in Chicago until about 1924, and the reaction of the public and the medical profession against its use following the many reports of the "radium dial" workers shortly afterward almost completely terminated its use. For this reason we are able to judge with fair accuracy the time of administration within a five-year period.

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* Postdoctoral Fellow, Medical Sciences, Atomic Energy Commission.

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## Table 1

FOURTEEN PATIENTS WHO HAD RADIUM CHLORIDE INTRAVENOUSLY AT THE ELGIN STATE HOSPITAL IN 1930-1931

| Patient | Dose†† (μg) | Age (1931) | X-ray changes | Est. Ra (γ ray) 6 mo.* (μg) | 12 mo.* (μg) | 240 mo.** (μg) | Est. Ra (Rn breath) 6 mo.* (μg) | 12 mo.* (μg) | 240 mo.† (μg) | Est. total-body Ra 6 mo.* (μg) | 12 mo.* (μg) | 240 mo. (μg) | Rn/Ra ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 110 | 23 | | | | .10 | | | .4 | | | .50 | .80 |
| | 150 | 27 | | 0.6 | 0.3 | .15 | 5.4 | 2.8 | (.4) | 6.0 | 3.1 | .55 | .73 |
| | 90 | 28 | | 0.5 | 0.6 | .24 | | | .4 | | | .74 | .62 |
| | 180 | 28 | | 0.8 | 0.09 | .25 | 5.9 | 1.8 | .6 | 6.7 | 1.9 | .85 | .70 |
| | 450 | 33 | | 1.6 | 1.3 | .30 | 16.1 | | .6 | 17.7 | | .90 | .67 |
| | 200 | 22 | | 0.5 | | .27 | | | .70 | | | .97 | .72 |
| | 260 | 25 | | 1.2 | 0.7 | .43 | 6.4 | 2.4 | .6 | 7.6 | 3.1 | 1.03 | .85 |
| | 200 | 31 | | 0.3 | 0.07 | .40 | 5.9 | 4.1 | 0.7 | 6.2 | 4.3 | 1.10 | .64 |
| | 110 | 18 | | 0.75 | 0.5 | .35 | 8.3 | 4.8 | 0.7 | 9.1 | 5.3 | 1.05 | .67 |
| | 150 | 22 | ++ | 1.0 | 0.9 | .67 | 7.2 | 2.5 | 1.1 | 8.2 | 3.4 | 1.77 | .62 |
| | 360 | 30 | | 1.1 | 0.9 | .60 | (1.8) | 5.7 | 1.2 | | 6.6 | 1.80 | .67 |
| | 250 | 23 | + | 1.1 | 0.9 | 1.25 | 5.8 | 4.2 | 1.6 | 6.9 | 5.1 | 2.85 | .57 |
| | 410 | 32 | + | 1.1 | | 1.45 | | | 2.3 | | | 3.75 | .61 |
| | 260 | 25 | | 2.3 | 1.8 | 2.45 | 12.0 | 3.3 | 4.5 | 14.3 | 5.1 | 6.95 | .64 |

*Schlundt, H., J. T. Nerancy, and J. P. Morris. 1933. The detection and estimation of radium in living persons. IV. The retention of soluble radium salts administered intravenously. Am. J. Roentgenol. Radium Therapy, 30(4): 515-522.

**Determinations by L. D. Marinelli, R. E. Rowland, P. F. Gustafson, May, 1951.
† Determinations by A. F. Stehney, W. P. Norris, H. F. Lucas, Jr., and T. Speckman, May, 1951.
} Final determinations are not complete.

†† Given 10 μg weekly.

The clinical study has consisted of the following procedures: estimation of total-body radium by radon breath and gamma-ray body measurements; clinical history; physical examination; hematological studies; serum calcium, phosphorus, and alkaline phosphatase determinations; Kahn test; dental examination, including dental X rays; and complete roentgenographic examination of the skeleton.

The amount of radium present in the body is the sum of the emanating and nonemanating fractions that are obtained by analysis of the radon content of the expired air and by measurements of gamma-ray activity from the patients' bodies. Tables 1 and 2 show estimates of the amount of radium present in the twenty-four patients studied. The techniques that we have used in estimating total-body radium* will be published at a later date.

For the convenience of the reader our estimates of the Elgin patients (Table 1) are compared with the physical measurements made by Schlundt et al., at six and twelve months after radium treatment. It is thought that the determinations of the estimation of gamma-ray activity (based on measurements with a Wulf-Hess quartz-fiber electroscope) are probably more accurate than their estimates based on the expired radon. They estimated the rate of expiration of radon by having the patient exhale into an ionization chamber, and they assumed a breathing rate of 7.5 liters per minute. We have found that unless the patient is breathing quietly and against little positive pressure, estimates of the amount of radon in the expired air may vary as much as 100 per cent or more. The expiration rate may also vary considerably for each patient.

The average retention of radium by the Elgin patients at six months after administration was estimated to be 4.3 per cent and at twelve months, 1.9 per cent. Our estimate of retained radium after twenty years was 0.8 per cent. These values were obtained by dividing the sum of the amount given by the sum of the estimates of retained radium. It should be noted in Table 1 that there was considerable individual variation from the average in the amount of radium given and the amount retained and that the patients who received the largest amounts did not show a greater percentage retained.

In the estimation of the amount of radium retained one is always confronted with the problem of how much of the radium was received by the patient and how much was adsorbed on the glass of the ampule and syringe. According to Schlundt et al., "Radium chloride in 10-$\mu$g doses dissolved in isotonic sodium chloride solution, having a volume of 2 cc, and carefully standardized, was injected at intervals of a few days to a week over periods

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* Dr. W. H. Johnston assisted us in the preliminary collection and determination of radon.

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Table 2

TEN PATIENTS WHO HAD RADIUM CHLORIDE EITHER ORALLY, INTRAVENOUSLY, OR INTRAMUSCULARLY, 1920-1930
(Studied November, 1950 - April, 1951)

| Patient | Years since Ra given | Present age | Amt. (μg) | Route | Est. Radium (μg) γ ray* | Rn** | Total | Rn/Ra ratio |
|---|---|---|---|---|---|---|---|---|
| [redacted] | 25 - 30 | 63 | unknown | P. O. | (.03) | .04 | (.07) | .75 |
| [redacted] | 26 - 27 | 42 | unknown | I. M. | (.10) | .4 | (.5) | (.80) |
| [redacted] | 20 | 51 | 160 | I. V. | (.20) | .5 | (.7) | (.71) |
| [redacted] | 26 | 56 | unknown | I. M. | .34 | .8 | 1.1 | .70 |
| [redacted] | ? | 79 | ? | ? | .70 | .8 | 1.5 | .53 |
| [redacted] | ? | 55 | ? | ? | .65 | 1.0 | 1.6 | .62 |
| [redacted] | 25 - 26 | 46 | unknown | P. O. | .80 | 1.1 | 1.9 | .58 |
| [redacted] | 27 | 52 | 200? | I. M. | 2.50 | 3.6 | 6.1 | .59 |
| [redacted] | 20 - 25 | 76 | 700-800 | I. V. | 4.70 | 5.5 | 10.2 | .54 |
| [redacted] | 25 - 30 | 67 | ? | ? | 4.60 | 6.8 | 11.4 | .62 |

*Determinations by L. D. Marinelli, P. F. Gustafson, and R. E. Rowland. November, 1950 - May, 1951. (Final determinations not complete.)

**Determinations by A. F. Stehney, W. P. Norris, H. F. Lucas, J. J. Liebner, and T. Speckman. November, 1950 - May, 1951. (Final determinations not complete.)

that ranged from two months to six months." Dr. Schlundt was considered by his contemporaries to be a very thorough and competent physicist and he may have taken into consideration this factor of adsorption.

Preliminary data have been collected on the excreta of nine patients at the Elgin State Hospital. We have found that the rate of elimination per twenty-four hours may be about 0.001 per cent of the radium present in the body. Determinations were made by the method reported by Russell, Lesko, and Schubert.[2] However, a longer and more controlled study will be necessary to establish accurately the coefficient of elimination.

In taking clinical histories and performing physical examinations on these patients, emphasis was placed on previous injury, tuberculosis, bone disorders, limitation or pain on movement of the joints, and bone tenderness. Only one of the fourteen mental patients was capable of supplying the details of a satisfactory history. All of their institutional records have been summarized, and the pertinent results are given in Table 3.

Serum calcium and phosphorus alkaline phosphatase results are given in Table 4. All Kahns were negative.

Hematological studies included a complete blood count, hematocrit, and sedimentation rate. In all patients with an estimated total-body radium content above 2 μg, the erythrocytes were slightly hypochromic, with minimal anisocytosis and poikilocytosis. In twenty-one of the twenty-four patients sedimentation rates were elevated above 20 mm in one hour (Table 5 for results of studies on each patient).

Since much attention has been given to the dental changes in radium-poisoned individuals, each patient has had a dental examination, including dental X rays (Table 3).* This is of special importance since dental X rays were the only X rays taken in the extensive survey of 228 of the "radium dial" workers in 1928.[3] In that study, dental changes were found in all workers who had gamma-ray readings of 4 μg or more of radium. It is hoped that some correlation may be made between the radium dial survey, scattered cases in the literature, the study recently completed by Aub, Evans, Hempelmann, and Martland,[4] and the dental and skeletal X-ray changes observed in our study.

Figures 1 and 2 show teeth that came from a patient with an estimated total-body radium content of 10 μg. The honeycombed appearance is reported to be seen frequently in radium-poisoned patients. It is non-specific and is seen occasionally in people of the older age groups.** The term "pink-tooth" is sometimes used to describe the external appearance

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* Dr. J. R. Blayney, Director Zoller Dental Clinic, University of Chicago, examined the patients in the Chicago Area, and Dr. Bernhard Mann, dentist at the Elgin State Hospital, examined the Elgin patients.

** Dr. J. R. Blayney, personal communication.

Table 3

SUMMARY OF THE CLINICAL HISTORY AND THE INTERPRETATION OF THE RADIOLOGICAL CHANGES

| Patient | No. | Present age | Est. Ra(μg) | Summary of clinical history | Roentgenological interpretation: Skeletal X rays** | Roentgenological interpretation: Dental X rays*** |
|---|---|---|---|---|---|---|
| [redacted] | 1 | 63 | .065 | Negative clinical history. | Questionable streaking. | Edentulous - otherwise within normal limits. |
| [redacted] | 2 | 43 | .50 | Negative hospital record. | Not complete. | Not complete. |
| [redacted] | 3 | 47 | .55 | Negative hospital record. | No lesion demonstrated. | Two areas of increased density 9 and 15 mm in diameter were present in the left mandible. One area of increased density 4 mm in diameter in right mandible. |
| [redacted] | 4 | 42 | .5 | Patient had poliomyelitis at 17 years of age with rather marked residual effects. | Streaking-femora, tibiae, fibulae. | Essentially within limits. |
| [redacted] | 5 | 48 | .74 | Negative hospital record. | Not complete. | Not complete. |
| [redacted] | 6 | 48 | .85 | Negative hospital record. | Streaking-fibulae. | A small number of areas of decreased density were noted in the right and left mandibles. |
| [redacted] | 7 | 53 | .90 | Fracture of the nasal bones 7/2/48; fracture of medial malleolus 10/25/48. Uneventful recovery. | Streaking-radiae; mottling-glenoid processes. | Unsatisfactory film - appears to be within normal limits. |
| [redacted] | 8 | 51 | .7 | In 1949, 17 years after receiving radium, pain and limitation of motion of the right leg. 4/13/51 - reconstruction operation of left hip. Core of bone removed and a segment of the right fibula inserted. Uneventful recovery to date. | Aseptic necrosis of the head of the right femur with partial collapse. | Edentulous - Essentially negative. |
| [redacted] | 9 | 42 | .97 | 12/8/31 tubercular abscess of the chest wall which gradually subsided- X rays of spine were negative at that time. | Not complete. | Not complete. |
| [redacted] | 10 | 45 | 1.03 | 1940 - pain on motion of the left hip; X ray of pelvis, lower sacral spine and left ankle revealed no pathology. No subsequent information. | Mottling-glenoid processes, streaking - radiae, ulnae, and fibulae. | Edentulous - Trabecular pattern appears to be within normal limits for patient edentulous for a considerable time. |
| [redacted] | 11 | 51 | 1.10 | In 1938 (age 39) difficulty with teeth, 7 extractions. No further note in record. | Mottling-left glenoid process; streaking left ulnar and radius. | Slight mottled appearance of the left mandible beneath the apex of first bicuspid. |
| [redacted] | 12 | 56 | 1.1 | In 1949, 23 years after receiving radium patient noted stiffness, limitation of motion, and pain in the right elbow especially while playing golf. X-ray changes were noted in the elbow in 1950. There has been a minimal increase in the severity of symptoms. Greater deterioration of the teeth the past 7-8 years. | Aseptic necrosis of the head of the right radius; mottling-glenoid processes and neck of left femur; streaking-radiae and fibulae. | Chronic periodontitis, resorption of alveolar bone and osteoporosis of the mandible. |



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Table 3

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Table 3 (Contd.)

| Patient | No. | Present age | Est. Ra(μg) | Summary of clinical history | Roentgenological interpretation: Skeletal X rays** | Roentgenological interpretation: Dental X rays*** |
|---|---|---|---|---|---|---|
| [redacted] | 13 | 52 | 1.05 | Negative hospital record. | Mottling-left glenoid process; streaking-fibulae. | No significant findings noted; however, motion of film when taken prevented adequate interpretation. |
| [redacted] | 14 | 45 | 1.5 | Patient does not know when he received radium. In 1939 small spicules of bone were noted to be coming from the left mandible. Condition progressed until 1941 when a graft was attempted unsuccessfully for non-union. There is little change noted in the non-union of the mandible in our recent studies. | Questionable mottling of glenoid processes. | Old defect in the left mandible with non-union. Trabecular pattern is unusual but probable within normal limits. |
| [redacted] | 15 | 55 | 1.65 | Patient does not know when she received radium. The past 2-3 years her teeth have deteriorated more rapidly and there was occasional tenderness around some of the teeth with exuding pus. She was told by her dentist in the winter of 1950 that it might be caused by radium. | Four areas decreased density in skull; mottling-glenoid processes; streaking-humeri, radiae, ulnae, fibulae, and tibiae. | Osteosclerosis and osteoporosis of the mandible with internal absorption of the roots of three teeth. |
| [redacted] | 16 | 46 | 1.9 | Fibrosarcoma of left foot, Reported as a special case. | (1948) - (Area of aseptic necrosis 10 x 15 mm in left tarsal scaphoid.) Twelve areas decreased density in skull; mottling-glenoid processes, heads of humeri and femori, and necks of femori. Streaking - right radius, tibiae, fibulae, and femori. (1951) - (Marked degenerative changes in the tarsal bones of the left foot - fibrosarcoma.) 22 areas of decreased density in skull; streaking in same bones as in 1948 with increase in size and number. | Not complete. |
| [redacted] | 17 | 42 | 1.77 | Patient was noted to walk with a waddling gait when first seen in 1950. Seemingly there was little pain on motion. Diagnosis of old osteochrondritis of the femora was made in 1940 by X ray. No record as to when patient began to have difficulty in walking. | Aseptic necrosis of the heads of femora with rather marked destruction of the normal configuration; streaking-tibiae and fibulae. | Questionable mottling of the inferior portion of the left mandible in the region of the angle. |
| [redacted] | 18 | 50 | 1.80 | Negative hospital record. | Streaking-radiae, fibulae, and left ulna. | Diffuse generalized mottling of both right and left mandibles. Most of the teeth missing. |



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Table 3 (Contd.)

| Patient | No. | Present age | Est. Ra(μg) | Summary of clinical history | Roentgenological interpretation: Skeletal X rays** | Roentgenological interpretation: Dental X rays*** |
|---|---|---|---|---|---|---|
| [redacted] | 19 | 43 | 2.85 | Dental reports 1931-35. Teeth in poor condition. | Aseptic necrosis of the head of the left humerus with some loss of normal configuration; mottling-left glenoid process and the head of the right humerus. | Edentulous - There is a slight increase in size in intertrabecular spaces near the right mental foramen otherwise trabecular pattern within normal range. |
| [redacted] | 20 | 52 | 3.75 | Patient has developed a slight limp of the left leg between August, 1950 and May, 1951. | Mottling of the head and neck of the left femur; streaking-left radius and ulna, right humerus, tibia, and fibula. | Appears to be edentulous except for two root fragments in the left mandible and two teeth in the right. There is a marked bilateral decrease in density in the bone of the right and left mandibles with almost no trabecular pattern. |
| [redacted] | 21 | 52 | 6.1 | In 1948, 22 years after receiving radium patient noted small spicules of bone extruding from left mandible. In the past three years six of these spicules have been noted and all teeth have had to be extracted. | 10 areas of decreased density in the skull; mottling-glenoid processes, head of right humerus, head and neck of left femur; streaking humeri, radiae, ulnae, tibiae, and fibulae. | Edentulous - with sclerosis of mandible. |
| [redacted] | 22 | 55 | 6.95 | Not complete. | Not complete. | Not complete. |
| [redacted] | 23 | 76 | 10.2 | In about 1936, two years after receiving radium, patient began to have considerable difficulty with his teeth. Over a period of years, all teeth and a large segment of the left mandible have been lost. In 1949, 15 years after taking radium pain in the right hip began which has slightly progressed in severity. | Aseptic necrosis on the weight bearing roof of the right acetabulum, 30 mm in diameter. Collapse of several vertebral bodies; 6 area of decreased density in skull; mottling-glenoid processes, marked streaking of the radiae, ulnae, tibiae, fibulae, and humeri. | Edentulous - segment of left mandible missing marked resorption in the right segment of the mandible. |
| [redacted] | 24 | 67 | 11.4 | Patient gave a very confused history about having radium 25-30 years ago. Apparently 10-15 years ago, she began to have pain in the hips - symptoms have progressed until now she is unable to walk. 5-10 years ago she began to have difficulty with her teeth - all have been lost as well as a large portion of the mandible. | X rays of pelvis taken in 1948 are the only films present; these show almost complete destruction of the heads of the femora. | Edentulous - large portion of right and left mandible missing. |

*Chicago Patients.

**Drs. Dallas B. Phemister, Paul C. Hodges, and Robert M. Potter and members of the Division reviewed these films.

***Dr. J. R. Blayney, Director Zoller Dental Clinic, University of Chicago, interpreted the dental X rays.



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Table 4

SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE VALUES**
(Normal Range: Ca, 9 - 11 mg %; P, 2.5 mg % (approximately);
Alk. Phos., 2 - 4 Bodansky units)

| Patient | No. | Present age | Est. total-body Radium (μg) | Serum calcium (mg %) | Serum phosphorus (mg %) | Alkaline phosphatase (Bodansky units) |
|---|---|---|---|---|---|---|
| [redacted] | 1 | 63 | .07 | 9.5 | 3.7 | 4.5 |
| [redacted] | 2 | 43 | .50 | 11.3 | 3.2 | 4.7 |
| [redacted] | 3 | 47 | .55 | 8.6 | 3.1 | 4.7 |
| [redacted] | 4 | 42 | .50 | 10.2 | 3.3 | 0.7 |
| [redacted] | 5 | 48 | .74 | 9.5 | 3.9 | 2.9 |
| [redacted] | 6 | 48 | .85 | - | 3.2 | - |
| [redacted] | 7 | 53 | .90 | 10.1 | 3.3 | 6.3 |
| [redacted] | 8 | 51 | .70 | 9.9 | 2.3 | 2.2 |
| [redacted] | 9 | 42 | .97 | - | 3.2 | 2.7 |
| [redacted] | 10 | 45 | 1.03 | 9.5 | 3.8 | 3.1 |
| [redacted] | 11 | 51 | 1.10 | 9.6 | 4.9 | 1.7 |
| [redacted] | 12 | 56 | 1.10 | 9.7 | 2.7 | 3.6 |
| [redacted] | 13 | 52 | 1.05 | 10.1 | 3.4 | 2.0 |
| [redacted] | 14 | 45 | 1.50 | 10.3 | 3.0 | 9.3 |
| [redacted] | 15 | 55 | 1.65 | 10.4 | 4.0 | 3.0 |
| [redacted] | 16 | 46 | 1.90 | 8.7 | 3.3 | 4.0 |
| [redacted] | 17 | 42 | 1.77 | 9.7 | 4.1 | 2.1 |
| [redacted] | 18 | 50 | 1.80 | 10.2 | 4.6 | 3.3 |
| [redacted] | 19 | 43 | 2.85 | 10.2 | - | - |
| [redacted] | 20 | 52 | 3.75 | 9.7 | 3.1 | 3.7 |
| [redacted] | 21 | 52 | 6.10 | 11.4 | 3.0 | 1.6 |
| [redacted] | 22 | 55 | 6.95 | 9.2 | 4.2 | 2.6 |
| [redacted] | 23 | 76 | 10.20 | 9.9 | 3.1 | 2.8 |
| [redacted] | 24 | 67 | 11.40 | 9.6 | 3.8 | 6.3 |

*Chicago Patients
**Determinations at the University of Chicago Clinics

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Table 5

HEMATOLOGICAL STUDIES** - 14 PATIENTS AT ELGIN STATE HOSPITAL WHO HAD $RaCl_2$ INTRAVENOUSLY - 1930-1931
10 PATIENTS IN THE CHICAGO AREA WHO HAD $RaCl_2$ INTRAVENOUSLY, INTRAMUSCULARLY, OR ORALLY - 1920-1930*

| Patient | Number | Estimated total body radium | Date | Erythrocyte count (per cu mm) | Hemoglobin (photoelectric method) (g/100 cc) | Leucocyte count (per cu mm) | Polymorphonuclear count (%) | Stabs (%) | Metas (Seen in 300 %) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Basophils (%) | Condition of red cells on differential | Mitotic lymphs (total seen) | Bilobed lymphs (total seen) | Immature lymphs (total seen) | Slightly immature lymphs | Atypical lymphs | Degenerating cells | Cells with vacuoles | Giant platelets | Atypical platelets | Sedimentation rate (mm in 1 hr.) | Hematocrit (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 1 | .07 | 1/31/51 | 467 | 13.7 | 5650 | 48 | - | - | 40 | 7 | 5 | - | Normal | - | - | - | - | occ. | | - | occ. | - | 35.0 | 41 |
| | | | 4/27/51 | 424 | 12.6 | | 49 | - | - | 47 | 2 | 1 | 1 | Normal | - | - | 1 | - | - | | - | - | - | - | - |
| | 2 | .4 | 8/29/50 | 491 | 14.5 | 25800 | 84 | 2 | 1 | 10 | 3 | 0 | 0 | Normal | 1 | - | 1 | - | - | 1 lymph | - | - | - | 30.0 | 47 |
| | | | 5/10/51 | 485 | 13.0 | 12600 | 63 | - | - | 32 | 2 | 2 | 1 | Normal | - | - | 1 | 1 | - | - | 1 Eosinophil | - | - | 24.0 | 15 |
| | 3 | .4 | 5/10/51 | 487 | 16.0 | 11000 | 68 | - | - | 26 | 4 | 1 | 1 | Normal | - | - | - | few | - | - | 2 Mono's | - | - | 6.0 | 46 |
| | 4 | .5 | 3/16/51 | 440 | 13.2 | 7700 | 53 | 2 | - | 34 | 4 | 6 | 1 | Slight anisocytosis | 2 | - | 1 | 3 | - | - | 1% Eosinophil | few | few | 22.0 | 44 |
| | 5 | .7 | 5/9/51 | 448 | 11.7 | 9500 | 88 | 1 | - | 32 | 4 | 2 | 2 | Normal | - | - | - | 2 | - | - | 1 Lymph | - | - | 42.0 | 11 |
| | 6 | .9 | 5/10/51 | 406 | 12.5 | 8600 | 67 | 1 | - | 25 | 2 | 4 | 1 | Normal | - | - | - | - | - | - | 2 Eosinophils | - | - | 47.0 | 37 |
| | 7 | .9 | 8/29/50 | 497 | 16.5 | 17000 | 88 | 1 | - | 9 | 2 | - | - | Normal | - | - | - | 4 | polys al toxic | | - | - | - | 35.0 | 47 |
| | | | 5/10/51 | 515 | 17.0 | 9600 | 70 | 2 | 1 | 24 | 3 | 1 | - | Normal | - | - | 1 | 2 | - | 2 Lymphs | - | - | - | 20.0 | 47 |
| | 8 | 1.0 | 11/17/50 | 467 | 12.7 | 11200 | 72 | - | - | 26 | 1 | 1 | - | Normal | - | - | - | - | - | - | 2 Lymphs | - | - | 27.0 | 39 |
| | 9 | 1.0 | 5/9/51 | 431 | 12.2 | 9500 | 82 | 1 | - | 44 | 1 | 2 | - | Slight anisocytosis, Few stippled rbc's | - | 1 | - | 3 | 2(transitionals) | | - | - | - | 42.0 | 41 |
| | 10 | 1.1 | 5/9/51 | 435 | 12.5 | 8100 | 53 | 1 | - | 33 | 2 | 10 | 1 | Normal | - | - | 1 | 2 | - | - | 2 Eosinophils | few | - | 27.0 | 41 |
| | 11 | 1.2 | 8/17/50 | 467 | 13.6 | 11800 | 55 | - | - | 42 | 2 | 2 | - | Normal | - | - | - | 1 | - | - | - | - | - | 42.0 | 44 |
| | | | 5/7/51 | 445 | 13.6 | 7200 | 75 | 1 | - | 23 | 1 | - | - | Normal | - | - | - | 3 | - | - | 1 Lymph | - | few | 29.0 | 42 |
| | 12 | 1.2 | 4/25/51 | 485 | 15.2 | 7700 | 51 | 3 | 1 | 44 | 1 | 1 | - | Normal | 3 Lymphs c̄ lg. azure gran. | | | 2 | - | - | - | - | - | 12.0 | 48.5 |
| | 13 | 1.2 | 8/22/50 | 472 | 14.5 | 12300 | 57 | - | - | 21 | 3 | 18 | 1 | Normal | - | - | - | - | - | - | - | - | - | 40.0 | 46 |
| | | | 5/7/51 | 420 | 13.0 | 8400 | 52 | 2 | - | 25 | 6 | 15 | - | Normal | - | - | - | 1 | - | - | 4 Eosinophils 1 Poly. | - | - | 48.0 | 41 |
| | 14 | 1.5 | 4/4/51 | 504 | 14.9 | 10000 | 61 | 3 | 1 Basophilic | 30 | 4 | 1 | 1 | Normal | 1 | 3 | - | 3 | - | - | 3 Lymphs | few | few | 13.0 | 52 |
| | 15 | 1.7 | 4/27/51 | 426 | 13.8 | 6400 | 64 | - | - | 34 | 1 | 1 | - | Normal | - | - | - | - | - | - | - | - | - | 32.0 | 43 |
| | 16 | 1.9 | 1/11/51 | 374 | 11.2 | 4900 | 59 | 2 | - | 36 | 1 | 2 | - | Marked anisocytosis Med. poikilocytosis Slight hypochromia | Polys toxic | | | - | few | | 1 Lymph With vacuoles | - | - | 54.0 | 36 |
| | | | 5/1/51 | 414 | 11.5 | 7550 | 63 | 2 | - | 30 | 2 | 3 | - | Slight anisocytosis and hypochromia | Polys toxic | | | 3 | - | 2 Lymphs | | | | | |
| | 17 | 2.2 | 8/17/50 | 450 | 12.2 | 6700 | 71 | - | - | 25 | 4 | - | - | Slight anisocytosis and hypochromia | - | - | - | few | - | - | - | - | - | 32.0 | 41 |
| | | | 5/7/51 | 493 | 12.2 | 10300 | 65 | - | - | 32 | 1 | 2 | - | Slight anisocytosis and hypochromia | - | 1 | - | 1 | - | - | - | - | - | 38.0 | 42 |
| | 18 | 2.4 | 8/17/50 | 435 | 13.2 | 8900 | 58 | - | - | 38 | 2 | 2 | - | Slight anisocytosis and hypochromia | - | - | - | few | - | 1 Lymph | - | - | - | 40.0 | 42 |
| | | | 5/7/51 | 435 | 13.5 | 6600 | 51 | - | - | 43 | 2 | 2 | 2 | Slight anisocytosis | 1 | - | - | 1 | - | - | - | - | - | 48.0 | 40 |
| | 19 | 2.8 | 5/10/51 | 440 | 12.9 | 9400 | 69 | 1 | 1 | 26 | 3 | 1 | - | Normal | - | - | 3 | few | - | - | 1 Lymph | - | - | 43.0 | 41 |
| | 20 | 4.1 | 8/22/50 | 424 | 11.5 | 6150 | 55 | 1 | - | 40 | 4 | 3 | 1 | Slight anisocytosis and hypochromia | - | - | - | 2 | - | - | - | - | - | 47.0 | 40 |
| | | | 5/7/51 | 430 | 12.2 | 8200 | 47 | - | - | 48 | 2 | 1 | 1 | | 1 Binucleated poly. Several lymphs c̄ large azure gran. | | | | | few polys | - | few | - | 41.0 | 39 |
| | 21 | 6.1 | 4/17/51 | 494 | 16.0 | 9750 | 68 | 1 | - | 31 | 1 | 2 | - | 1 Polychromatic red cell | - | - | - | - | occ. | - | 1 Poly 1 Eosinophil | - | - | 20.5 | 50.5 |
| | 22 | 7.2 | 5/9/51 | 382 | 11.5 | 7600 | 64 | 1 | - | 25 | 2 | 8 | - | Moderate anisocytosis and hypochromia | - | - | - | - | - | - | 1 Mono 1 Eosinophil | - | - | 37.0 | 38 |
| | 23 | 10.2 | 3/13/51 | 356 | 11.9 | 10600 | 67 | 7 | 1 | 23 | 1 | 1 | 1 | Moderate anisocytosis Slight poikilocytosis and hypochromia | Few toxic polys | | | 4 | - | - | Few polys and Eosinophils occ. lymph | - | - | 38.0 | 35 |
| | 24 | 12.3 | 5/10/51 | 485 | 14.0 | 7000 | 68 | - | - | 27 | 4 | 1 | - | Normal | - | - | 1 | 2 | - | 2 Lymphs | 2 Lymphs | - | - | 32.0 | 44 |

*Chicago patients.
**Hematological studies made by Ellen Skirmont.



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of these teeth; the pinkish cast being caused by decreased density between the red pulp and the outer enamel covering. One of our patients [redacted] No. 15) was referred to us for study because the dentist* suspected radium poisoning after observing a "pink-tooth" condition.

Complete roentgenographic examination of the skeleton has been made on nineteen of the twenty-four patients. The radiological changes noted in the bones of these patients have been divided into four groups:

1) Small well-defined areas of decreased density that occur principally in the skull and range from 1 to 5 mm in diameter (Figure 3).

2) Areas of increased density and decreased density that occur relatively close to each other and give a "mottled" or "moth-eaten" appearance. There are two principal areas in which mottling has been noted. One is in the heads and necks of the femora, where there are usually well-defined areas of increased density between 1 and 2 mm in diameter. There may or may not be adjacent areas of decreased density. This also occurs in the heads of the humeri to a lesser degree. The second area is in the glenoid processes of the scapulae whose appearance may be described as more "moth-eaten" than mottled. There is usually a rearrangement of the trabecular pattern, with focal areas of reduced density and irregularly increased trabecular markings (Figures 4 and 5).

3) Longitudinal areas of decreased density that occur in the shafts of the long bones give a streaked appearance. Minimal changes are rather difficult to evaluate because at present we are unable to establish a well-defined normal range (Figure 6).

4) Varying degrees of distortion of normal configuration and destruction of bone were seen in seven of the twenty-four cases. We will use the term "aseptic necrosis"[5] (Figure 7), primarily in a descriptive manner, in reference to these changes.

Of the nineteen cases in which dental and complete skeletal X rays have been made, there have been changes compatible with the diagnosis of aseptic necrosis in seven, a partial loss of the mandible in two cases, and nonunion of the mandible in one; fifteen of the nineteen cases had changes that we have described as either well-defined areas of decreased density, mottling, or streaking.

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* Dr. O. H. Moldal.

The regularity of the skeletal changes in these patients suggests that they were produced by radium. It is to be stressed, however, that these alterations are nonspecific, and such factors as injury, faulty blood supply, and other poorly understood factors may have produced the changes by themselves or in conjunction with radium. More information will be needed before any definite conclusions can be made.

We have been very fortunate in having Dr. Dallas B. Phemister, Professor Emeritus of Orthopedic Surgery, University of Chicago, Dr. Paul C. Hodges, Head of the Department of Radiology, University of Chicago, and Dr. Robert M. Potter, Associate in Radiology, Northwestern University, give their time in reviewing X-ray films and the benefit of their experience in the interpretation of roentgenographic and pathological changes caused by aseptic necrosis and radium. The consistency of the skeletal changes was observed by Dr. Potter and the author in the review of the radiographs.

## 3. MALIGNANCY

One case of malignancy has been found in the study. This is present in patient [redacted] (No. 16, Table 3). About twenty years ago, during a period of several weeks, the patient received water containing an unknown amount of radium for migratory polyarthritis. It was given orally at the rate of 15 drops, 3 times daily. In 1947, sixteen years after taking the radium water, pain began to occur in the left foot whenever she walked. In 1948 X rays of the foot were taken, and a diagnosis of "aseptic necrosis of the tarsal bones of the foot" was made. In 1951, the patient was studied in our clinic, and the total-body radium content was estimated to be 1.9 μg. Because of the marked changes in the bones of the foot, a biopsy was obtained and a fibrosarcoma was diagnosed from the histological section. The leg was amputated 15 cm below the knee, and the patient made an uneventful recovery. However, pain of increasing severity is present in the shoulders, spine, and remaining foot. Laboratory data on this patient are given below:

| Date | | |
|---|---|---|
| 2-17-48 | Sternal marrow | Erythroblastic hyperplasia |

| Date | RBC | Hg | Smear of peripheral blood |
|---|---|---|---|
| 2-3-48 | 5,300,000 | 12 | |
| 1-11-51 | 3,740,000 | 11.2 | Polymorphonuclear leucocytes-toxic |
| 5-1-51 | 4,140,000 | 11.5 | Polymorphonuclear leucocytes-toxic |

| Date | Calcium | Phosphorus | Alkaline phosphatase |
|---|---|---|---|
| 2-6-48 | 10.3 | 5.4 | 5.2 |
| 2-16-48 | 10.4 | 5.7 | 5.3 |
| 3-6-48 | 10.4 | 5.4 | --- |
| 1-11-51 | 8.7 | 3.3 | 4.0 |

## 4. ESTIMATES OF RADIUM IN AN AMPUTATED LEG

Estimates of the nonemanating fraction of radium in the amputated leg of patient [redacted] were made at different times and by various methods. Two days after amputation (2-22-51) the gamma activity of the whole leg was found to be equivalent to 0.022 $\mu$g of radium by means of scintillation counting. The soft tissues were then removed, and the bones of the leg were sealed in a glass container in order to measure the gamma-ray activity of the radium in equilibrium with its daughters. This was done on April 30, 1951, and the total Ra content was found to be 0.04 $\mu$g. The nonemanating fraction of radium of most of the available bones was measured again by inserting them singly in a high-pressure ionization chamber (5-27-51), and the sum was found to be 0.0204 $\mu$g (Table 6). It is seen also in Table 6 that, except for the tumor area, the average concentration per gram of wet bone as determined by gamma-ray activity does not differ in any one bone by more than 25 per cent from the average of the total amount of bone removed. Although the agreement between these two types of measurement is satisfactory, it remains to be established whether the agreement is fortuitous or is indicative of an approximate equipartition of Ra in the free emanating and nonemanating form.

This similarity in concentration was found in some measurements on total radium content of samples of bone weighing from 0.4 to 1.5 g. The data are presented in Table 7. It may be seen that the average concentration of the four samples assayed is $9.45 \times 10^{-5}$ g of radium per g of wet bone, which is in good agreement with the average obtained in Table 7 where the ratio of nonemanating radium to total radium is taken into consideration. It should also be noted that the low radium content in the tumor area is consistent in both types of measurements.

However, comparison between the total average radium content of the bones of the amputated leg and the average concentration in the skeleton as obtained by in vivo measurements, reveals some significant discrepancies (Table 8). It will be noticed that, on the average, the concentration of total radium in the leg bones is about one third that calculated from the in vivo measurements on the patient and the assumed weight of her skeleton. While

Table 6

ESTIMATION OF THE NONEMANATING RADIUM CONTENT OF THE BONES OF THE AMPUTATED LEG OF PATIENT [redacted] BASED UPON VALUES OBTAINED USING THE HIGH-PRESSURE GAMMA CHAMBER AND VIBRATING-REED ELECTROMETER*

| Bone | Weight of wet bone (g) | Estimated total radium content ($\mu$g) | $\gamma$-ray activity in $\mu$g of Ra per g wet bone |
|---|---|---|---|
| Tibia | 90 | .0050 | $5.5 \times 10^{-5}$ |
| Fibula | 45 | .0027 | $6.0 \times 10^{-5}$ |
| Talus<br>Calcaneus | 78 | .0039 | $4.9 \times 10^{-5}$ |
| Tumor area | 45 | .0021 | $2.8 \times 10^{-5}$ |
| Distal foot | 166 | .0077 | $4.2 \times 10^{-5}$ |
| | Total 424 | Total .0204 | Av. $4.8 \times 10^{-5}$ |

*Determinations by W. P. Norris and W. B. Looney.

## Table 7

### ESTIMATION OF THE RADIUM AND CALCIUM CONTENT OF SPECIMENS TAKEN FROM THE VARIOUS BONES OF THE AMPUTATED LEG OF PATIENT [redacted]

W. P. Norris, T. Speckman, L. Woodruff, and B. Lawrence

| A<br>Bone | B<br>Wet wt. (g) | C<br>Ash wt. (g) | D<br>Est. total radium content (alpha activity)* ($\mu$g) | E<br>Est. total radium** content (emanation method) | F<br>Radium † ($\mu$g/g wet bone) $\left(\frac{D}{B}\right)$ | G<br>Calcium content (g) | H<br>$\frac{\mu g\ Ra}{g\ Ca}$ $\left(\frac{D}{G}\right)$ | I<br>Est. †† total-body radium ($\mu$g Ra) | J<br>% of calcium in ash |
|---|---|---|---|---|---|---|---|---|---|
| Tibia (cortical bone 10 cm below knee) | 0.617 | 0.255 | $5.54 \times 10^{-5}$ | $6.68 \times 10^{-5}$ | $9 \times 10^{-5}$ | .0987 | $5.6 \times 10^{-4}$ | .48 | 38.7 |
| Calcaneus cross section of principally trabecular bone | .544 | 0.197 | $6.27 \times 10^{-5}$ | $5.80 \times 10^{-5}$ | $11 \times 10^{-5}$ | .0738 | $8.50 \times 10^{-4}$ | .73 | 37.5 |
| Cuneiform | .442 | .101 | $5.29 \times 10^{-5}$ | | $12 \times 10^{-5}$ | .0377 | $14.00 \times 10^{-4}$ | 1.20 | 37.3 |
| Tumor area (tarsal bones) | 1.545 | .258 | $9.04 \times 10^{-5}$ | $14.6 \times 10^{-5}$ | $5.8 \times 10^{-5}$ | .0913 | $9.90 \times 10^{-4}$ | .85 | 35.4 |

* The rapid radiometric assay for radium and its application to uranium ore process solutions, by D. P. Ames, J. Sedlet, H. H. Anderson, and T. P. Kohman, in "The Transuranium Elements," Seaborg, Katz, and Manning, N.N.E.S., Div. IV, Vol. 14B. paper 22.70, page 1700.

** Radon emanating from the ashed samples in column C was determined by a Lindemann-Ryerson electrometer, and the radium content estimated from these values.

† The radium content of the specimens in column D was divided by the wet weight of bone in column C. This column was inserted to compare the estimates of concentration of radium per gram of wet bone by this method with those obtained by placing the entire bone in a high-pressure gamma chamber (see Table 6).

†† Dr. Lisco's standard 70-kg man is estimated to have 1 kilogram of calcium. On this basis, the skeleton of this patient was assumed to have 860 grams of calcium. The estimates of total-body radium given in this column were obtained by multiplying the values in column H by 860.

Table 8

AVERAGE ESTIMATED CONCENTRATION OF RADIUM IN BONES OF THE AMPUTATED LEG AND ITS RELATION TO THE ESTIMATED TOTAL-BODY RADIUM CONTENT (PATIENT [redacted]

| Method of estimation average concentration of radium | Est. radium $\mu g$ / g wet bone | Est. $\gamma$-ray activity (nonemanating radium-$\mu g$ Ra/g wet bone) | Est. total-radium content ($\mu g$ radium per g of wet bone) | % of est. total-body radium ($\gamma$-ray plus radon breath) |
|---|---|---|---|---|
| 1. Est. total-body radium ($\gamma$ ray and radon breath) | $\frac{1.9}{6000}$ | - | $3.17 \times 10^{-4}$ | - |
| 2. Scintillation counter | $\frac{.022}{475}$ | $4.64 \times 10^{-5}$* | $.93 \times 10^{-4}$ | 29.2 |
| 3. High pressure $\gamma$ chamber | $\frac{.0204}{424}$ | $4.81 \times 10^{-5}$* | $.96 \times 10^{-4}$ | 30.3 |
| 4. Average $\alpha$ activity on 5 bone specimens (Column F, Table 7) | | | $.94 \times 10^{-4}$ | 29.8 |
| 5. Average determination on same specimens (4) by emanation method (Column $\frac{E}{D}$, Table 7) | | | $1.03 \times 10^{-4}$ | 37.5 |
| 6. Average estimation based on calcium content of bone (Column H, Table 7) | | | $9.5 \times 10^{-4}$ $\mu g$ radium per g calcium | 35.4 |

*We are assuming the Rn/Ra ratio for this bone is 50%.



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a small part of this difference is due to nonskeletal radium,* the discrepancy is too large for experimentation and indicates that the leg bone of this patient took up radium in smaller proportion than the average. This is consistent with results published in the literature.(6)

## 5. INITIAL EFFORTS TO CORRELATE RADIUM DISTRIBUTION WITH THE RADIOLOGICAL CHANGES BEING SEEN IN THIS STUDY

After radiographs were made of the patient's [redacted] amputated fibula (Figures 8-12), sections were taken from the streaked areas of decreased density. The bone changes appear to be reasonably well-defined areas of degeneration running approximately parallel to the haversian systems.

Microscopic examination of cross sections of the fibula shows central canals whose diameters range from normal up to almost the entire diameter of the haversian system. Dr. Phemister has suggested that the central canals may have increased in size by gradual bone resorption as seen in bone degeneration. The large areas of bone destruction may have resulted in fusion of adjacent central canals. The gross, microscopic and radiological changes are shown in Figures 13 through 16.

The only histological sections we have at the present time were taken from the upper end of the tibia. Dr. Phemister, Dr. C. Howard Hatcher, Professor of Orthopedic Surgery, University of Chicago, and Dr. F. Wassermann have received these sections and consider the changes to be consistent with those seen in dead and dying bone. There was, however, minimal evidence of regeneration. The degenerative changes seen in these histological sections are similar to those seen in the fibula (Figures 13 and 13A).

Radioautographs of bone taken from the tibia and including the cortex and trabeculae have been prepared by Dr. J. S. Arnold.(7) Although the sections are longitudinal and oblique, they show similar areas of destruction and variation in size of the central canals in the tibia as previously seen in the fibula. Radium distribution in these sections was very irregular. Large areas of the cortical and trabecular bone contained almost no alpha tracks or were entirely free of them. In other areas the radium was relatively concentrated. We are as yet unable to establish any direct relationship between the radium distribution and the destructive changes. Some haversian systems have destructive changes with almost no alpha tracks, others have destruction with alpha tracks concentrated along the periphery of the central canal. Some haversian systems appear relatively normal with radium present either in the manner described or more evenly distributed (Figures 14 to 16).

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* Dr. A. F. Stehney found that the concentration of radium in soft tissue was about 1/200 that of the bones. This may not be too reliable because bone dust may have been carried into the tissues at the time of operation.

## 6. CONCLUSION

The most significant findings in this study have been the roentgenographic findings. Seventeen of the nineteen patients had changes in bone density, and in eight of the nineteen, changes in normal configuration of bone were present. No direct relationship was observed between the roentgenographic changes or symptomatology and the amount of radium remaining in the body. This observation has also been made by Dr. L. H. Hempelmann who was concerned with the clinical aspects of a similar investigation of twenty-eight people by Aub, Evans, Hempelmann, and Martland (to be published soon). All patients having 1 μg or more radium in their bodies had roentgenographic changes. One patient who had an estimated total-body radium content of 0.5 μg had minimal roentgenographic changes.

It would seem that radium plus an unknown factor or factors combine to produce bone degeneration. In discussing the roentgenographic changes with Drs. Joseph C. Aub, Dallas B. Phemister, Shields Warren, and Howard Hatcher, we find that all have considered that the effect of radium on the blood supply to the bone may be an important factor in producing the changes.

Dr. Paul C. Hodges has consented to have the members of the Department of Radiology of the University of Chicago look for changes similar to those being seen in these patients. Most of the heads of the Radiological Departments in the hospitals of Chicago are familiar with this study. It is planned to meet with these men and invite them to conduct a similar study. This will serve two purposes:

1) It will provide further information on the normal range of skeletal changes in people in this age group.

2) It will help locate more persons who have had radium.

Dr. C. Howard Hatcher has consented to examine specimens of a similar nature in an effort to determine whether there are any differences or similarities in the histological changes being seen in the patients who have had radium and those who have other degenerative bone diseases.

Specimens of the amputated leg of the patient [redacted] are being prepared for serial sectioning. An attempt will be made to map simultaneously the alpha tracks and the histological changes to permit the construction of a three-dimensional plastic model. This may provide a better understanding of radium distribution as well as offer a means of calculationg the amount of ionizing radiation necessary to produce bone changes.

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